mpca

COVID-19 Therapeutics - Educational Session for Health Center Clinicians

FEBRUARY 01-28, 2022

Presenters

1. **Natasha Bagdasarian MD, MPH, FIDSA**
   Chief Medical Executive
   Michigan Department of Health and Human Services

2. **William Fales, MD, FACEP, FAEMS**
   State Medical Director
   Division of EMS and Trauma
   Michigan Department of Health and Human Services

3. Lindsay Petty, MD
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COVID-19 Therapeutics

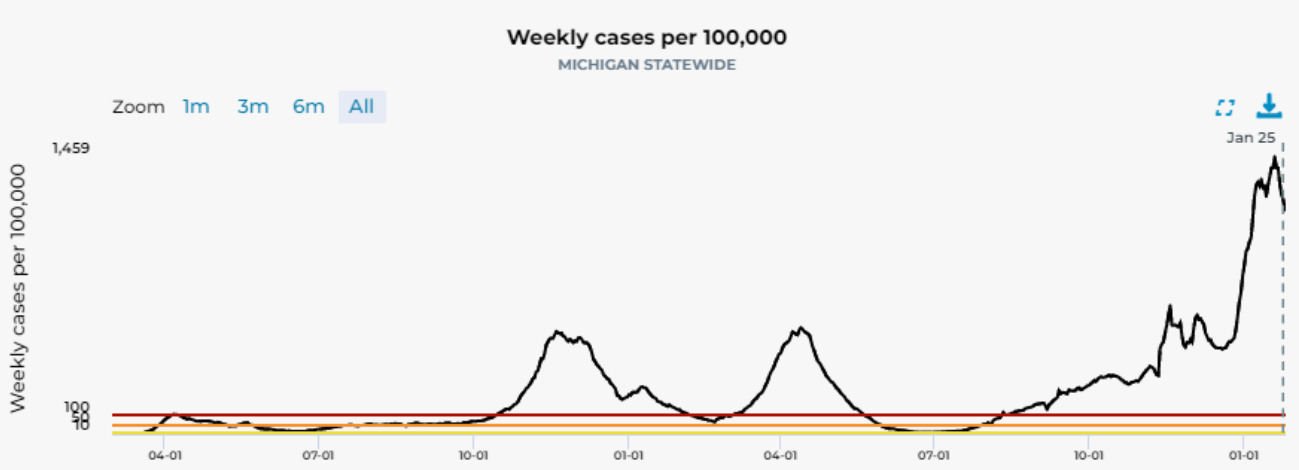
January 28, 2022

New Cases

Jan 19 - Jan 25

1,177.6
weekly cases per 100,000 population

117,606
weekly cases



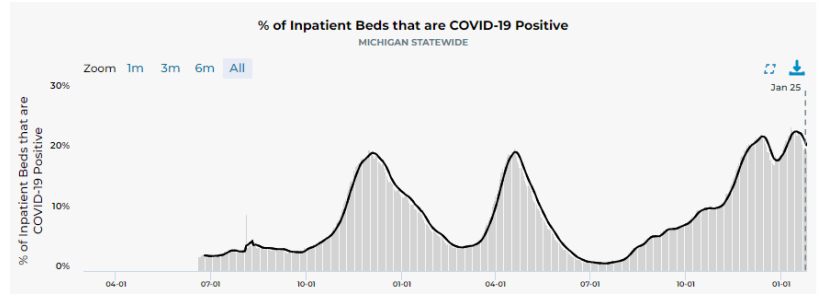
Hospital Capacity

Jan 19 - Jan 25

20.9%
beds for COVID

405.7
beds per million with COVID

2k
beds per million (COVID + non-COVID)



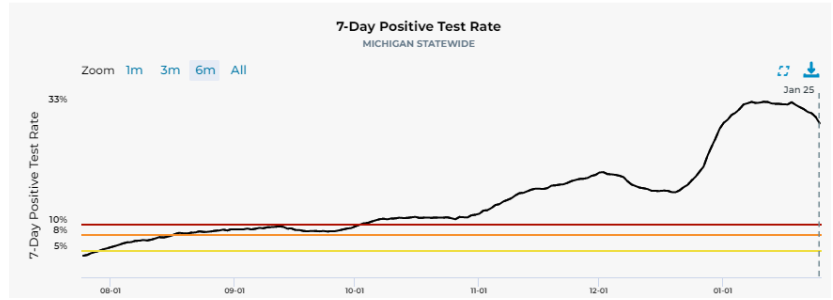
Test Positivity

Jan 19 - Jan 25

29.3%
positive tests

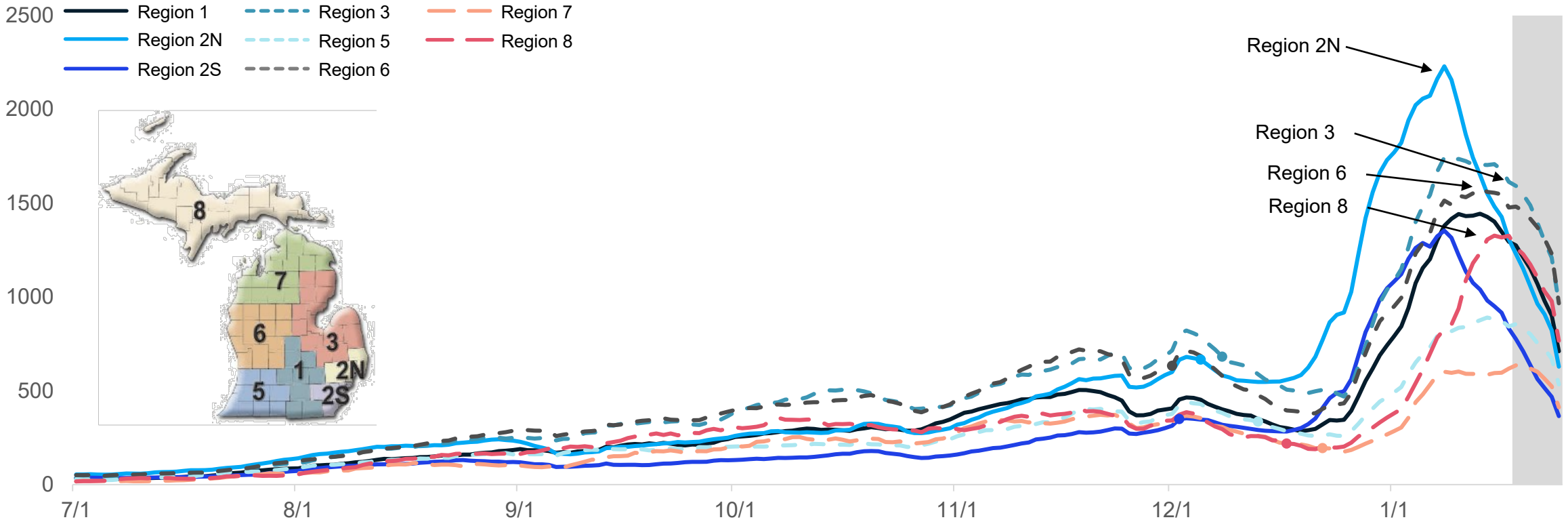
5.4K
daily tests administered per million

2 weeks
Jan 07 - Jan 21



Case Rate Trends by Emergency Preparedness Region

Daily new confirmed and probable cases per million by Region (7-day rolling average)

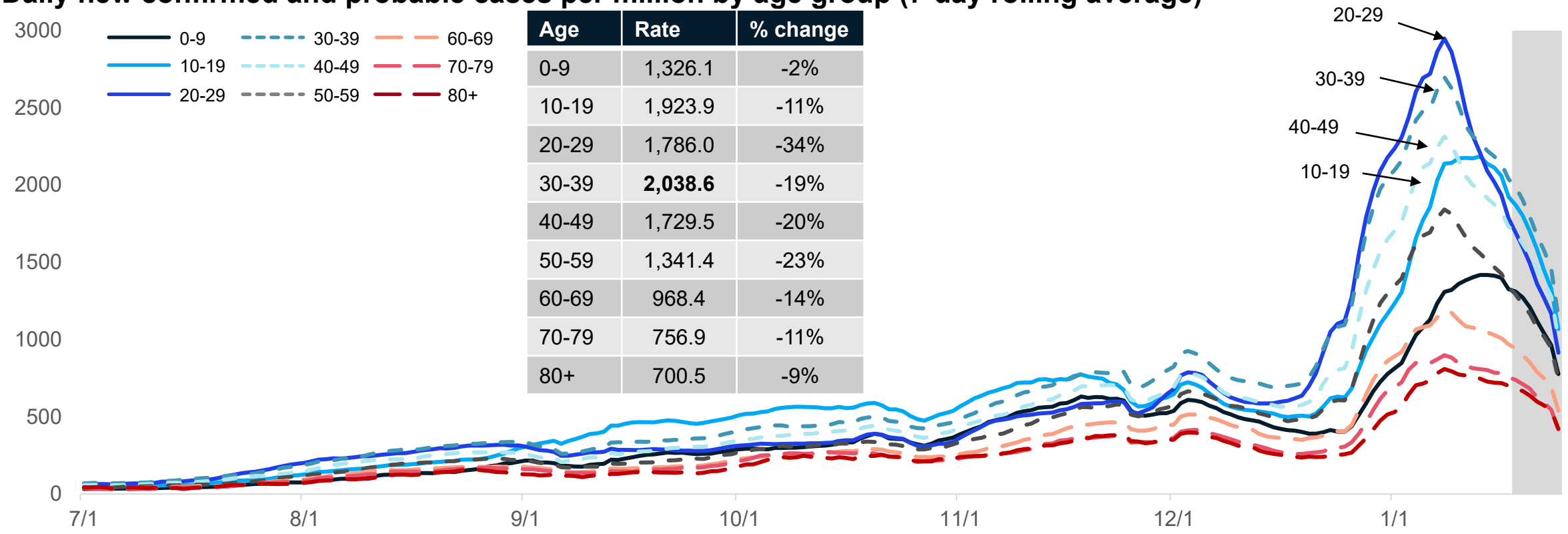


- Case rate trends for most preparedness regions plateaued the past week (through 1/17)
- Regions 2N and 2S are declining whereas Region 8 (upper peninsula) is increasing
- Case rates are highest in Region 3, followed by Region 6, and then Regions 8, 2N, and 1

Note: Case information sourced from MDHHS and reflects date of onset of symptoms
Source: MDHHS – Michigan Disease Surveillance System

Case Rate Trends by Age Group

Daily new confirmed and probable cases per million by age group (7-day rolling average)



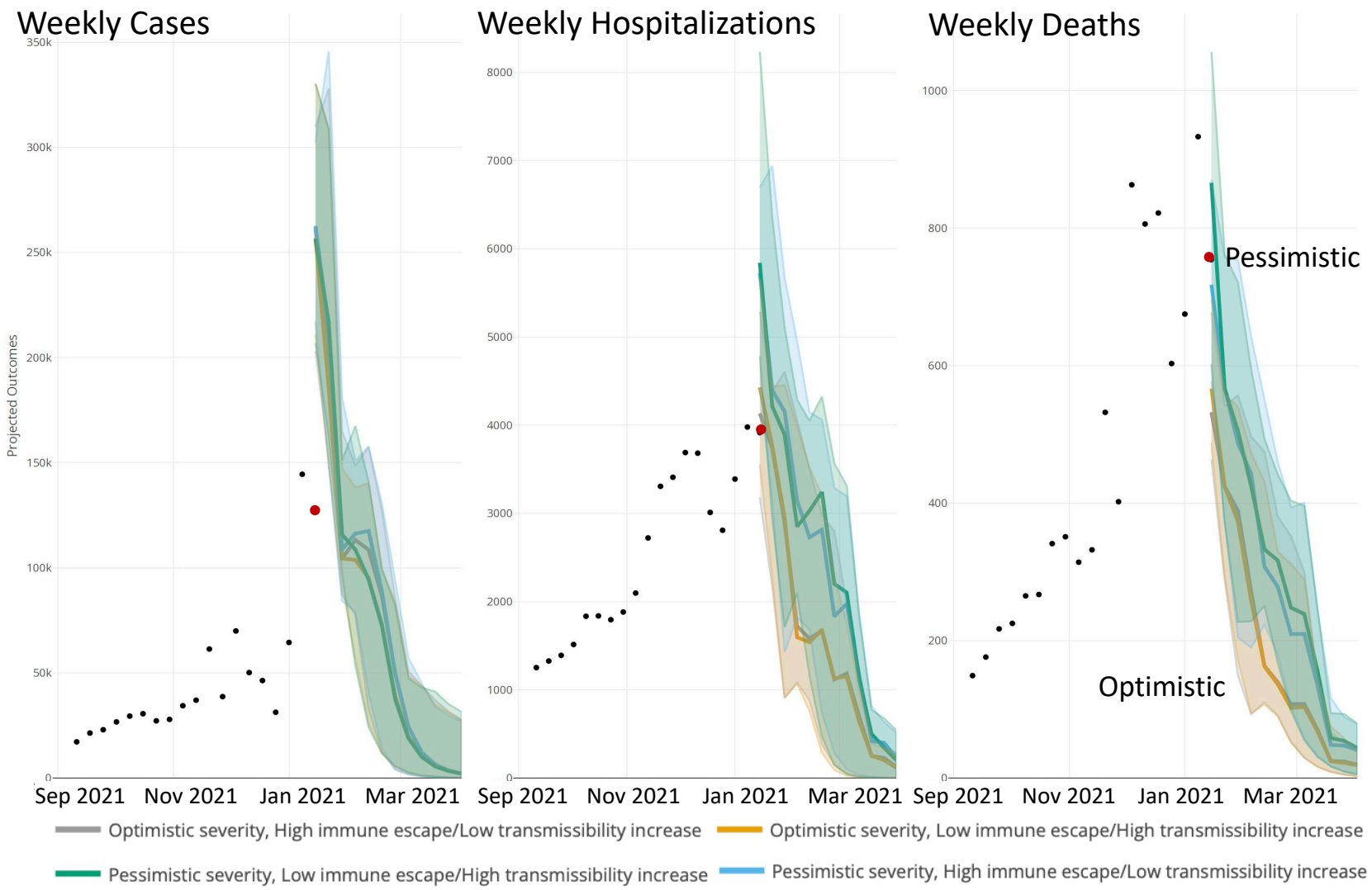
Age	Rate	% change
0-9	1,326.1	-2%
10-19	1,923.9	-11%
20-29	1,786.0	-34%
30-39	**2,038.6**	-19%
40-49	1,729.5	-20%
50-59	1,341.4	-23%
60-69	968.4	-14%
70-79	756.9	-11%
80+	700.5	-9%

- Case rate trends for most age groups saw decreases increases over the past week
- Case rates by onset date for all age groups are between 700 and 2,040 cases per million (through 1/17)
- Case counts and case rates are highest for 30-99-year-olds this week

Note: Case information sourced from MDHHS and reflects date of onset of symptoms
Source: MDHHS – Michigan Disease Surveillance System

Where are we headed: models project further increases in cases, hospitalizations, and deaths for Michigan

- Updated Model Scenarios (Round 12)
- Suggest we are near or at peak levels for all three metrics
- Deaths appear more consistent with the more pessimistic scenarios so far
- Round 11 projections are similar, but suggest potential for 1-2 additional weeks to peak for hospitalizations and deaths in the more pessimistic scenarios
- All projections suggest that cases, hospitalizations and deaths will still be high over the coming weeks, even if declining



Source: COVID Modeling Scenario Hub. Uncertainty levels: 50%

Guiding Principles

To prioritize **equity** in each of the following objectives

01

Prevent death and severe outcomes

Prioritize uptake of vaccinations and booster doses.

Protect the most vulnerable

- Mitigate risks in congregate settings using all available tools.

Maximize early access to testing and therapeutics.

02

Protect health care capacity (from hospitals to first responders to LTFS)

Reduce community spread during a surge through all available tools.

Reduce severity of cases, need for ICU/ventilators through vaccines and therapeutics.

03

Keep vital infrastructure (schools, corrections) functioning safely, while planning for recovery

Establish a new normal at every phase of the pandemic.

- Utilizing all available tools and the concept of "risk budget“.

Provide tools to the public to protect themselves.

- Including OTC testing and instructions for isolation and contact tracing.

MDHHS
Michigan Department of Health & Human Services

Vaccines

Protect against severe outcomes

Boosters are more important than ever, and available for individuals 12+

Masks, Distancing & Ventilation

Prevent spread

Well-fitting, high-quality masks in all indoor public or crowded settings are more important than ever

Tests

Prevent spread

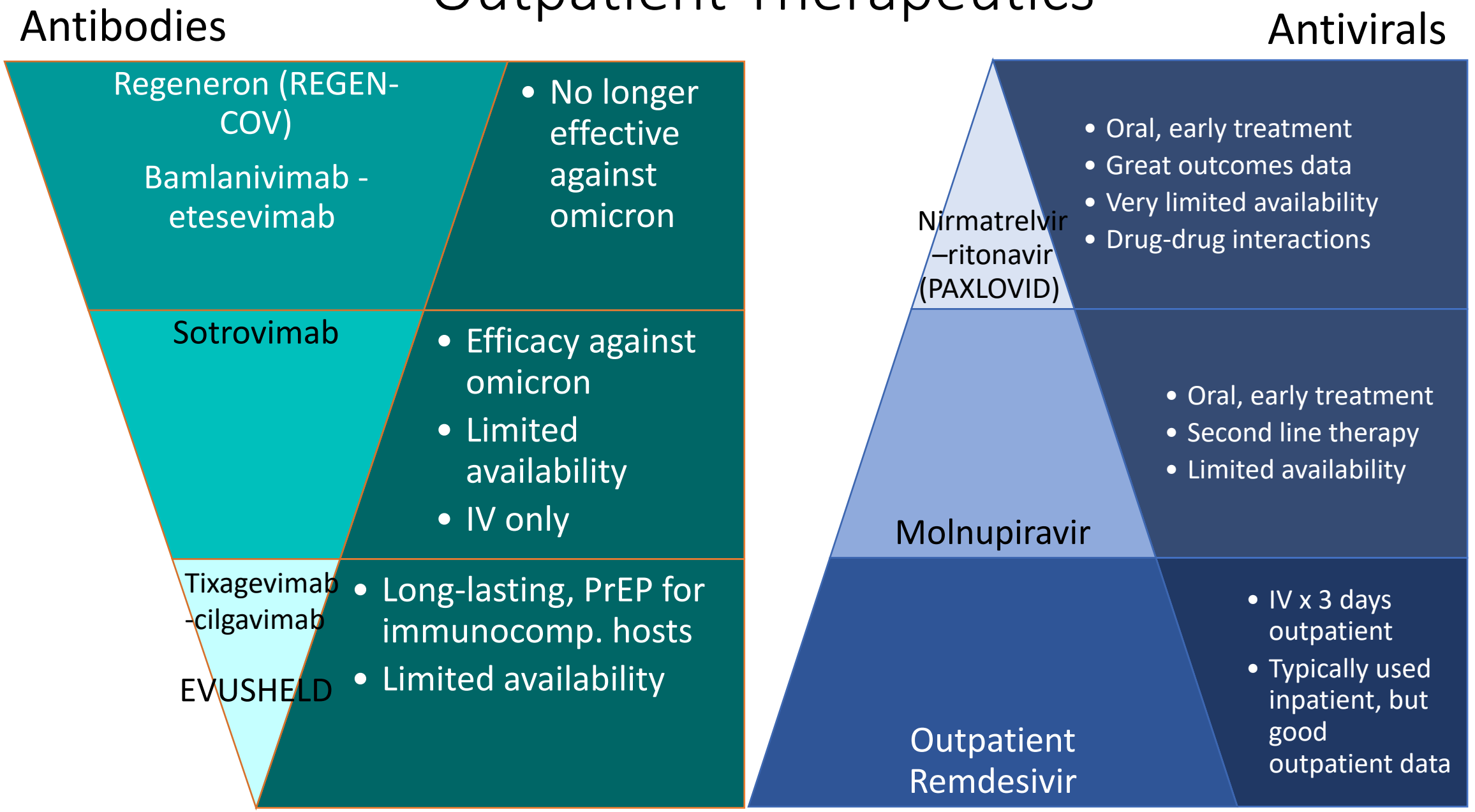
We encourage testing before gatherings, with symptoms, and after exposure

Treatment

Protect against severe outcomes

Oral antivirals and monoclonal antibody infusions are available

Outpatient Therapeutics



eTable 1. Comparison of Treatment Options for High-Risk Nonhospitalized Patients With Mild to Moderate COVID-19

	Nirmatrelvir-ritonavir[1]	Sotrovimab[2]	Remdesivir[3]	Molnupiravir[4]
Efficacy (prevention of hospitalization or death)	• Absolute risk reduction: 6.3%→0.8% • Relative risk reduction: 88% • NNT: 18	• Absolute risk reduction: 7%→1% • Relative risk reduction: 85% • NNT: 17	• Absolute risk reduction: 5.3%→0.7% • Relative risk reduction: 87% • NNT: 22	• Absolute risk reduction: 9.7%→6.8% • Relative risk reduction: 30% • NNT: 35
Advantages	• Highly efficacious • Oral regimen • Ritonavir studied (safe) in pregnancy	• Highly efficacious • Monoclonal antibodies typically safe in pregnancy • Few/no drug interactions	• Highly efficacious • Studied in pregnancy • Few/no drug interactions	• Oral regimen • Not anticipated to have drug interactions
Disadvantages	• Drug-drug interactions	• Requires IV infusion followed by 1-h observation	• Requires IV infusion on 3 consecutive days	• Low efficacy • Concern: mutagenicity • Not recommended in pregnancy/children

Abbreviations: IV, intravenous; NNT, number needed to treat.

January 14, 2022

COVID-19 Therapeutics for Nonhospitalized Patients

Rajesh T. Gandhi, MD[1]; Preeti N. Malani, MD, MSJ[2,3]; Carlos del Rio, MD[4]

Author Affiliations | Article Information

JAMA. Published online January 14, 2022. doi:10.1001/jama.2022.0335

eTable 2. Outpatient Therapies and Potential Patient Populations

Medication	Examples of patient population
Nirmatrelvir, 300 mg, plus ritonavir, 100 mg, orally twice daily for 5 d	• Patient not taking interacting medications • Administer as soon as possible and within 5 d of symptom onset
Sotrovimab, 500 mg, intravenous infusion	• Patient taking medication that interacts with nirmatrelvir-ritonavir • Patient able to come to health care facility • Administer as soon as possible and within 10 d of symptom onset
Remdesivir intravenous infusion, 200 mg (day 1) and 100 mg (days 2 and 3)	• Patient in health care facility or through home infusion service • Administer as soon as possible and within 7 d of symptom onset
Molnupiravir, 800 mg, orally twice daily for 5 d	• Adult patient not able to be treated with one of the options above • Not pregnant (if given during pregnancy, shared decision-making) • Administer as soon as possible and within 5 d of symptom onset

January 14, 2022

COVID-19 Therapeutics for Nonhospitalized Patients

Rajesh T. Gandhi, MD[1]; Preeti N. Malani, MD, MSJ[2,3]; Carlos del Rio, MD[4]

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Priority Eligibility Criteria for COVID-19 Outpatient Therapy (Revised January 19, 2022)

Tier	Eligibility Criteria	Paxlovid PO	Sotrovimab[4] IV	Remdesivir IV	Molnupiravir PO
	Preference Per NIH Treatment Guidelines	→			
	Treatment must be started within (X) days of symptoms:	5 days	10 days	7 days	5 days
	Availability:	• Limited Statewide -Select Meijer • -Select pharmacies • Selected FQHCs • Selected THCs	• Statewide -Variable sites	• Statewide -Variable sites	• Limited Statewide -Select Meijer -Select pharmacies
1A	• Any age (per applicable EUA or FDA approval) with moderate to severe immunocompromise regardless of vaccine status **or** • Age≥75 YO and not up to date on COVID vaccines[1]	Yes	Yes	Yes	Alternative[2]
1B	• Age 65-74 YO, not up to date on COVID vaccines[1], and with MI priority risk factor[3] • Pregnant and not up to date on COVID vaccines[1]	Yes	Yes	Yes	Alternative[2]
2	• Age 65-74 YO and not up to date on COVID vaccines[1] • Age <65 YO, not up to date on COVID vaccines[1]with MI priority risk factors[3]	Yes	Yes[5]	Yes	Alternative[2]
3A	• Age ≥75 YO and up to date on COVID vaccines[1] • Age 65-74 YO, up to date on COVID vaccines[1], and with MI priority risk factors[3]	Not currently eligible	Not currently eligible	Not currently eligible	Yes
3B	• Age 65-74 YO, up to date on COVID vaccines[1], and with CDC risk factors	Not currently eligible	Not currently eligible	Not currently eligible	Not currently eligible
4	• Age ≥65 YO and up to date on COVID vaccines[1] • Age <65 YO, up to date on COVID vaccines[1], and with CDC risk factors	Not currently eligible	Not currently eligible	Not currently eligible	Not currently eligible

mAb=monoclonal antibody, FQHC=Federally Qualified Health Centers, THC=Tribal Health Centers

[1]Those not up to date include those who are not vaccinated, have not completed their initial series, and those not boosted, when eligible as per Stay Up to Date with Your Vaccines | CDC

[2]Alternatives include Paxlovid, sotrovimab, remdesivir that are available in a timely manner

[3]MI priority risk factors include:

- Obesity (BMI ≥ 35)
- Chronic respiratory disease (e.g., COPD, moderate or severe asthma requires daily inhaled corticosteroid, bronchiectasis, CF, ILD)
- Pregnancy (Note: In pregnancy, molnupiravir should not be used and Paxlovid and remdesivir should be used with caution when sotrovimab is unavailable)
- Chronic Kidney Disease (stage III, IV, or end stage CKD-GFR) (special considerations with Paxlovid)
- Cardiovascular disease (e.g., HTN, valvular disease, CVA, PAD, CHF)
- Diabetes

[4]Sotrovimab is currently the only mAb therapy active against the Omicron variant and is in limited supply. Other mAb products may be considered, if indicated.

[5]Use in lower tiers should be done only when higher tiers are able to be treated in a timely manner. Higher tier patients are a priority.

COVID-19 Outpatient Therapy

Options for Michigan Clinicians

William Fales, MD, FACEP, FAEMS
State Medical Director
Division of EMS and Trauma

Disclosures

- Discussing the use of unapproved medications
  - FDA Emergency Use Authorization
  - Paxlovid, sotrovimab, molnupiravir, Evusheld

- Use of brand names
  - Paxlovid, Evusheld

Current COVID-19 Outpatient Therapeutics

Treatment of Mild to Moderate COVID-19

- Monoclonal Antibody Therapy
  - **Sotrovimab (IV)**
- Antiviral Therapy
  - **Paxlovid (PO)**
  - **Remdesivir (IV)**
  - **Molnupiravir (PO)**

Prophylaxis

- Pre-Exposure Prophylaxis Monoclonal Antibody
  - **Evusheld (IM)**
- Post-Exposure Prophylaxis
  - N/A

Preference of NIH Recommendations for Therapy Based on Eligibility / Availability

- **Paxlovid** (within 5 days of symptom onset), then
- **Sotrovimab** (within 10 days of symptom onset), then
- **Remdesivir** (within 7 days of symptom onset), then
- **Molnupiravir** (within 5 days of symptoms, no alternatives)

- Source: https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/

PO Paxlovid (nirmatrelvir and ritonavir)

- **Mechanism:** Antiviral - protease inhibitor
- **Efficacy:** EPIC-HR (randomized controlled) Trial (N=2,246)
  - Relative reduction in hospitalization or death: 88% (95% CI: 75%, 94%)
  - All cause 28-day mortality: Paxlovid: 0/1,039 vs placebo: 12/1,046 (1.1%)
  - Versus Omicron ? – Expected to be effective
- **Renal:**
  - Moderate (GFR 30-60): Adjust dose
  - Severe (GFR <30): Contraindicated
- **Hepatic:** Severe (Child-Pugh Class C): Contraindicated
- **Pregnancy:** Inadequate human data. Consider with caution
- **Drug Interactions:** Many related to CYP3A
  - Resource: https://www.med.umich.edu/asp/pdf/outpatient_guidelines/Paxlovid-DDI.pdf

Source: **Factsheet for Healthcare Providers Emergency Use Authorization for Paxlovid™**

Paxlovid Current Eligibility

- **FDA EUA Core Requirements**
  - ≥12 YO, +SARS-2CoV, within 5 days of symptoms, high-risk for progression
- **MI Current Priority Eligibility**: Tier 1, 2, (and now) >>> 3A
  - Immunocompromised, regardless of vaccination status
  - Age ≥75 YO, regardless of vaccination status
  - Age 65-74 YO, not up to date with COVID vaccine (including not boosted)
  - Age 65 to 74 YO, up to date with COVID vaccine, and with MI High Risk Factors
  - Pregnant and not up to date with COVID vaccine (sotrovimab preferred) – Unknown risk vs benefit discussion
  - Age >12 YO, not up to date with COVID vaccine and with MI High Risk Factors
- **MI High Risk Factors for Disease Progression**
  - Obesity (BMI ≥ 35)
  - Chronic respiratory disease (e.g., COPD, moderate or severe asthma, bronchiectasis, CF, ILD)
  - Chronic Kidney Disease (stage III, IV, or end stage CKD-GFR)
  - Cardiovascular disease (e.g., HTN, valvular disease, CVA, PAD, CHF)
  - Diabetes

Dosing of PAXLOVID

(see full Fact Sheet for Healthcare Providers)

- PAXLOVID is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir must be co- administered with ritonavir.
- Initiate PAXLOVID within 5 days of symptom onset.
- Administer orally with or without food.
- Dosage:
  - 300 mg nirmatrelvir (two 150 mg tablets) with
  - 100 mg ritonavir (one 100 mg tablet)
  - with all three tablets taken together twice daily for 5 days.
- **Dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min)**
  - 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days.

Source: **Factsheet for Healthcare Providers Emergency Use Authorization for Paxlovid™**

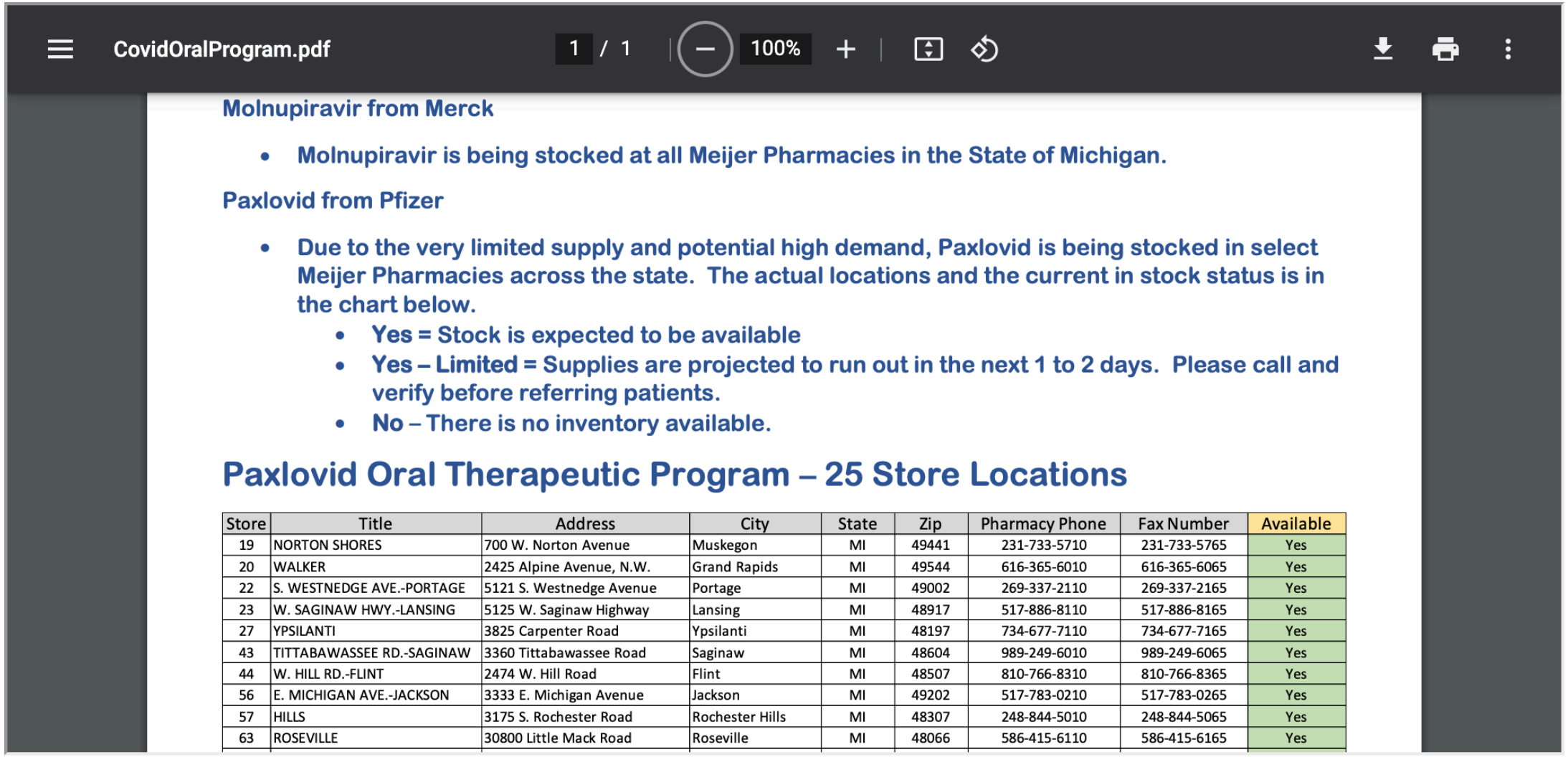
Paxlovid Availability

- 1,600 to 2,480 patient courses per 2 weeks
- Available at:
  - Selected Federally Qualified Health Centers
  - Selected Tribal Health Centers
  - 25**>>>47** Meijer Pharmacies
  - Selected retail pharmacies in Meijer remote area
  - To find a Paxlovid dispensing pharmacy:
    - https://rx.meijer.com/covid19/therapeuticprogram

Supply NOT a Problem!

COVID-19 Oral Therapeutic Program

This page is intended for Healthcare Professionals in the State of Michigan, providing the projected in stock status of the oral COVID-19 therapeutic products at Meijer Pharmacies.



Molnupiravir from Merck

- **Molnupiravir is being stocked at all Meijer Pharmacies in the State of Michigan.**

Paxlovid from Pfizer

- **Due to the very limited supply and potential high demand, Paxlovid is being stocked in select Meijer Pharmacies across the state. The actual locations and the current in stock status is in the chart below.**
  - **Yes = Stock is expected to be available**
  - **Yes – Limited = Supplies are projected to run out in the next 1 to 2 days. Please call and verify before referring patients.**
  - **No – There is no inventory available.**

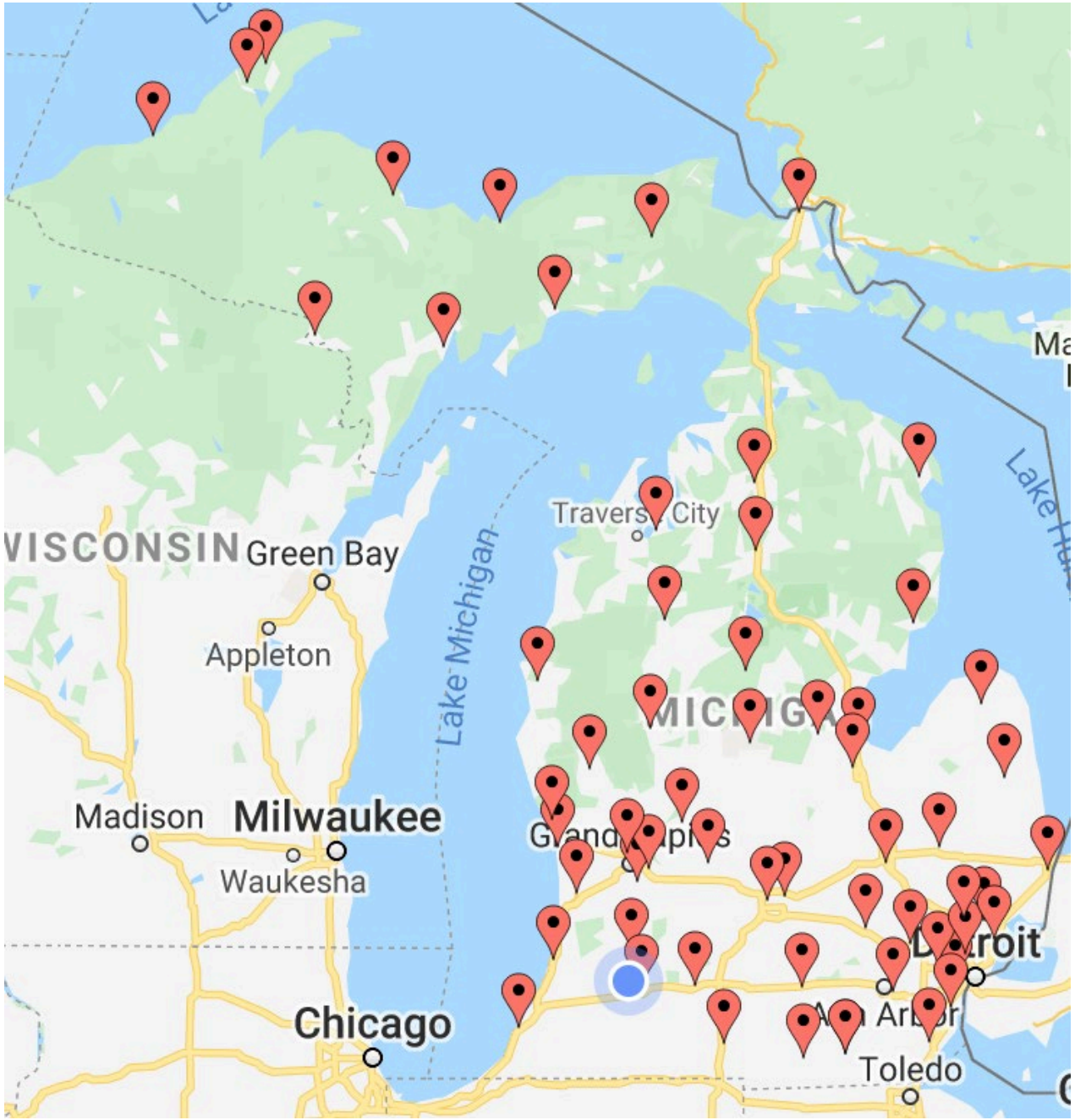
Paxlovid Oral Therapeutic Program – 25 Store Locations

Store	Title	Address	City	State	Zip	Pharmacy Phone	Fax Number	Available
19	NORTON SHORES	700 W. Norton Avenue	Muskegon	MI	49441	231-733-5710	231-733-5765	Yes
20	WALKER	2425 Alpine Avenue, N.W.	Grand Rapids	MI	49544	616-365-6010	616-365-6065	Yes
22	S. WESTNEDGE AVE.-PORTAGE	5121 S. Westnedge Avenue	Portage	MI	49002	269-337-2110	269-337-2165	Yes
23	W. SAGINAW HWY.-LANSING	5125 W. Saginaw Highway	Lansing	MI	48917	517-886-8110	517-886-8165	Yes
27	YPSILANTI	3825 Carpenter Road	Ypsilanti	MI	48197	734-677-7110	734-677-7165	Yes
43	TITTABAWASSEE RD.-SAGINAW	3360 Tittabawassee Road	Saginaw	MI	48604	989-249-6010	989-249-6065	Yes
44	W. HILL RD.-FLINT	2474 W. Hill Road	Flint	MI	48507	810-766-8310	810-766-8365	Yes
56	E. MICHIGAN AVE.-JACKSON	3333 E. Michigan Avenue	Jackson	MI	49202	517-783-0210	517-783-0265	Yes
57	HILLS	3175 S. Rochester Road	Rochester Hills	MI	48307	248-844-5010	248-844-5065	Yes
63	ROSEVILLE	30800 Little Mack Road	Roseville	MI	48066	586-415-6110	586-415-6165	Yes

Paxlovid

- Available at 47 Meijer Pharmacies
- Additional retail pharmacies
- Proximity
  - ~90% of population with Paxlovid dispensing site in county
  - >98% of population with site in county or adjacent county
- Expanded home delivery, if needed

- https://rx.meijer.com/covid19/therapeuticprogram



Monoclonal Antibody Therapy

- For treatment of mild to moderate COVID-19 in high-risk patients
  - Treatment within 10 days of symptom onset
- November 2020 to Present over 90,000 patient courses
  - >4,500 hospitalizations prevented (NNT=~20)
  - >1,800 deaths prevented (NNT=~50)
- Medications
  - ~~Bamlanivimab and etesevimab~~
  - ~~Casarivimab and indevimab (REGEN-COV)~~
  - **Sotrovimab**

Inactive against Omicron

Active against Omicron

Sotrovimab

- **Mechanism:** Monoclonal antibody targeting spike protein
- **FDA EUA Indication:**
  - Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
  - Adults and pediatric patients (12 years of age and older weighing at least 40 kg)
  - Positive results of direct SARS-CoV-2 viral testing, and
  - Who are at high risk for progression to severe COVID-19, including hospitalization or death.
- **Limitations**
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).
- **Patients meet the Michigan High Risk Criteria** (currently Tier 1 and 2)

Source: https://www.fda.gov/media/149534/download

Sotrovimab

- Administration
  - IV infusion over at least 30 minutes
  - Post-infusion observation of at least 60 minutes
  - FDA considering IM route option
- Supply: Limited (<1,300 per week, vs >6,000 per week)
- Availability
  - mAb infusion sites
    - Hospitals/EDs
    - Infusion clinics
    - EMS
    - Urgent care/clinics
    - Long-term care facilties
  - Additional info: www.Michigan.gov/covidtherapy

IV Remdesivir

- **Mechanism:** inhibit the SARS-CoV-2 RNA-dependent RNA polymerase
- **Efficacy**: PINETREE Trial 87% reduction in deaths or hospitalizations compared to placebo (N=562) when given within 7 days
  - Source: Gottlieb, et al., NEJM, Dec 22, 2021
- **Renal:** Contraindicated if GFR <30 mL/min
- **Hepatic:** Baseline liver function studies
- **Pregnancy:** Inadequate human data. Consider with caution.
- **Drug Interactions:** Inadequate human data.

IV Remdesivir

- **NIH Treatment Panel Recommendations**
  - **Remdesivir 200 mg** IV on Day 1, followed by **remdesivir 100 mg** IV daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg
- **MI Current Priority Eligibility**: Tier 1 and 2
  - Immunocompromised, regardless of vaccination status
  - Age ≥65 YO, not up to date with COVID vaccine (including not boosted)
  - Pregnant and not up to date with COVID vaccine (sotrovimab preferred)
  - Age >12 YO, not up to date and with MI High Risk Factors for disease progression
- **Challenges**
  - IV x3 days
  - Medication cost: ~$2,000 (Currently Medicare Part B)

PO Molnupiravir

- **Mechanism:** Antiviral **(**mutagen)
- **Efficacy**: Relative reduction in hospitalizations or deaths
  - 50% pre-delta>>>30% total>>>24% delta>>>Omicron?
- **Renal:** N/A
- **Hepatic:** N/A
- **Pregnancy:** Contraindicated
- **Drug Interactions:** None known

Source: https://www.fda.gov/media/155054/download

PO Molnupiravir

- **FDA EUA Core Requirements**
  - ≥18 YO, +SARS-2CoV, within 5 days of symptoms, high-risk for progression
  - **Only use when other therapies are unavailable / delayed**
- **MI Current Priority Eligibility**: Tier 1, 2, 3A, (and now) **>>> 4**
  - Immunocompromised, regardless of vaccination status
  - Age ≥65, regardless of vaccination status
  - Age 18 to 64 YO, regardless of vaccination status, and with ~~MI High~~ CDC at Risk Factors for disease progression

Molnupiravir Dosing and Availability

- Dosing
  - 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.
  - Take molnupiravir as soon as possible after a diagnosis of COVID19 has been made, and within 5 days of symptom onset.
  - Contraindicated in pregnancy
- Availability
  - Molnupiravir is currently available at all Meijer Pharmacies in MI
  - Available at 20 retail pharmacies in areas remote from a Meijer Pharmacy
  - https://rx.meijer.com/covid19/therapeuticprogram

Source: https://www.fda.gov/media/155054/download

Evusheld (Tixagevimab Plus Cilgavimab) for Pre-Exposure Prophylaxis

- FDA EUA: Moderate to severe immune compromise or past severe reaction to COVID vaccine
- Mechanism: Long-acting monoclonal antibody
- Administration: 2 IM injections every 6 months
- Availability
  - <1,500 patient courses in first 2 weeks allocated to MI
  - Distributed to 17 healthcare systems for high-risk ptients
- Prioritization: MI adopted modified 2-tiered NIH prioritization

Additional Info: www.Michigan.gov/covidtherapy

Thanks

mddhs-covid-therapies@Michigan.gov

www.Michigan.gov/covidtherapy

Practical Tips for Oral COVID-19 Therapeutic Prescribing

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Nicholas Dillman, PharmD

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When prescribing think about:

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1. Eligibility Criteria → Comorbidities
2. Day of symptom onset = Treatment window
3. Age, weight
4. Renal Function, Liver Function
5. Pregnancy
6. DDI
7. Patient consent and EUA FAQ
8. Meijer Location (or available FQHC) for your patient

Eligibility criteria

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Think about the following patient factors to determine which agent to chose:

		Paxlovid (oral)	molnupiravir (oral)	sotrovimab (IV)
		age ≥12, ≥40kg, Sx ≤5 days[1] eGFR >/= 30, no Class C liver 88% RR	age ≥18 Sx ≤5 days[1] No pregnancy 30% RR	age ≥12, ≥40kg, Sx ≤10 days[1] 85% RR
1a	-Moderate to severe immunocompromise regardless of vaccine status (any age) -or- -Age ≥75 and ***not*** up-to-date w/vaccines[2]	**YES** *unless DDI contraindicated or Sx >5 days	Alternative (if patient cannot get Paxlovid nor mAb)	**YES** *if Paxlovid is contraindicated due to DDI
1b	--Pregnant and ***not*** up-to-date w/vaccines[2] --Age 65-74 ***not*** up-to-date w/vaccines[2] and w/one priority risk factor[3]	**YES**	Alternative *unless pregnant* (if patient cannot get Paxlovid nor mAb)	**YES**
2	-Age 65-74 ***not*** up-to-date w/vaccines[2] -Age <65 ***not*** up-to-date w/vaccines[2] and w/one priority risk factor[3]	**YES**	Alternative (if patient cannot get Paxlovid nor mAb)	**YES**
3a	-Age ≥75 up-to-date w/vaccines[2] -Age 65-74 up-to-date w/vaccines[2] and w/one priority risk factor[3]	NO	**YES**	**YES- if higher tiers can be treated in a timely manner; lower priority**

[1]First day of symptoms counts as day 0 (i.e., if symptoms started on Monday (day 0), Saturday would be day 5)
[2] up-to-date w/vaccines = a person has received all recommended COVID-19 vaccines, including any booster dose(s) when eligible
[3]Priority risk factors include: Chronic lung disease, Cardiovascular disease, Diabetes, Chronic kidney disease, BMI ≥35

Paxlovid (ritonavir boosted nirmatrelvir) MD Decision-Making Process

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1. Eligibility Criteria:

- Moderate to severe immunocompromise regardless of vaccine status (any age)
- Age ≥65 and ***not*** up-to-date w/vaccines
- Pregnant and ***not*** up-to-date w/vaccines
- Age <65 ***not*** up-to-date w/vaccines and w/one priority risk factor

2. Symptoms ≤ 5 days

3. Age ≥ 12, weight ≥ 40kg

4. Renal Function, Liver Function

- Contraindicated: eGFR <30; Child-Pugh Class C liver disease
- eGFR 30-59 dose reduced: Nirmatrelvir 300 mg (2x 150 mg tabs) + ritonavir 100 mg (1x 100 mg tab) twice daily x5 days
- eGFR ≥60 no adjustment Nirmatrelvir 150 mg + ritonavir 100 mg twice daily x5 days

5. Pregnancy – not studied, unknown risk vs benefit talk

Paxlovid (ritonavir boosted nirmatrelvir) MD Decision-Making Process

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6. DDI:

- Interactions with many medications. Contraindications for some, adjustments needed for others:
  - Liverpool Drug Interactions Website
  - https://www.med.umich.edu/asp/pdf/outpatient_guidelines/Paxlovid-DDI.pdf

7. Consent:

- Review the following with the patient:
  - Potential adverse events (dysgeusia, diarrhea, myalgia, hypertension, hepatic injury)
  - Pertinent drug interactions and med adjustments
  - FDA has authorized emergency use of Paxlovid but not FDA approved
- Provide FDA Fact Sheet for Patients/Caregivers via email or patient portal:
  - Fact Sheet Paxlovid

8. Meijer Location (or available FQHC) for your patient

- $0 co-pay to patients

Paxlovid (ritonavir boosted nirmatrelvir) Prescribing details

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- Availability of drug? Select Meijer pharmacies, other select pharmacies, select FQHCs. Updated link with active drug availability here:
  - https://rx.meijer.com/covid19/therapeuticprogram
- Send eRx in MiChart to one of those select Meijer pharmacies. **In script, document that the patient has:**
  - Positive test
  - Date of symptom onset
  - Specific reason for eligibility (i.e. immunocompromised, Lupus on cellcept and prednisone)

Paxlovid Drug-Drug Interactions

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- **Nirmatrelvir and ritonavir = CYP3A inhibitor**
- Drugs metabolized by CYP3A can be INCREASED
  - Harmful high levels
- Drugs that induce CYP3A may DECREASE Pax
  - decrease PAXLOVID therapeutic effect
- Each DDI needs to be evaluated for severity and **options for avoidance**
  - Many DDIs can be accommodated with simple adjustments
  - E.g., statins, calcium channel blockers, alpha-1 blockers, etc.

Paxlovid Drug-Drug Interactions

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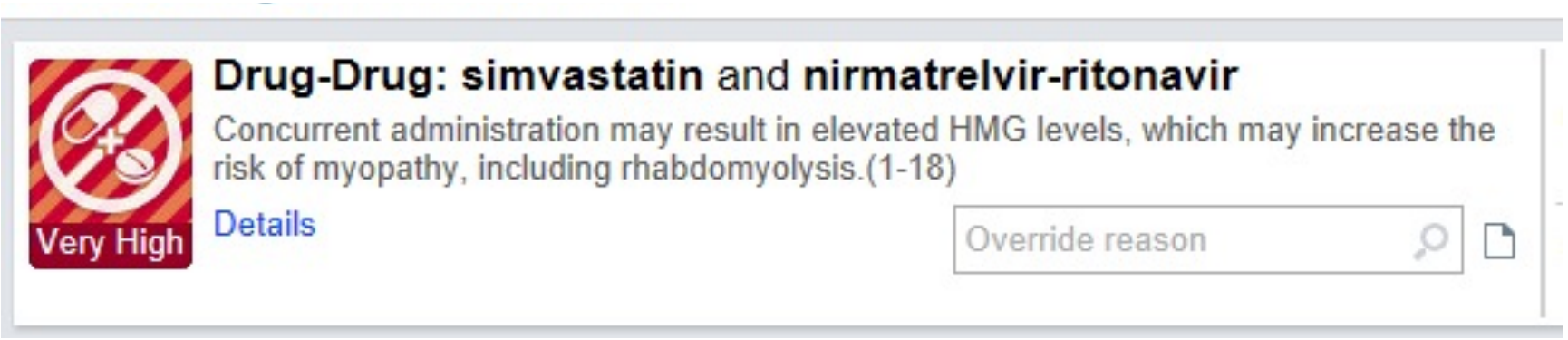
- **76 yo M with h/o CHF and hyperlipidemia. Simvastatin on his drug list.**
- **When you go to prescribe Paxlovid, you may see:**



- **Don't stop there.**
- **Use other resources:**
  - **Liverpool**
  - **MM Paxlovid DDI Table**

Paxlovid Drug-Drug Interactions: Liverpool

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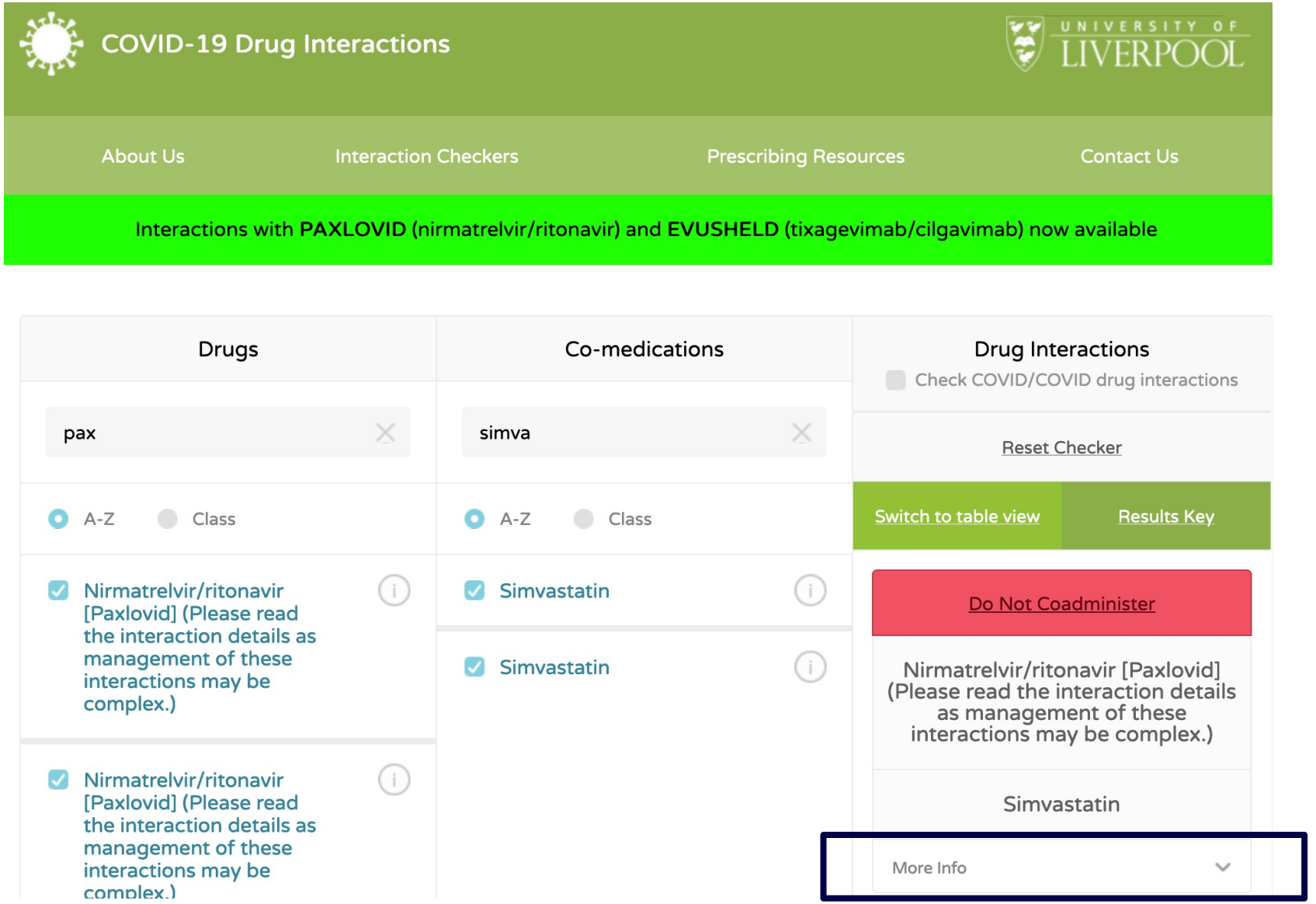
https://www.covid19-druginteractions.org/



Paxlovid Drug-Drug Interactions (cont.)

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- https://www.covid19-druginteractions.org/

Do Not Coadminister
Nirmatrelvir/ritonavir [Paxlovid] (Please read the interaction details as management of these interactions may be complex.)
Simvastatin

Quality of Evidence: Very Low
Summary:
Coadministration of simvastatin and potent CYP3A4 inhibitors, such as ritonavir, is contraindicated due to potential for serious reactions such as risk of myopathy including rhabdomyolysis. Given the duration of nirmatrelvir/ritonavir treatment, simvastatin should be stopped. Restart simvastatin 3 days after the last dose of nirmatrelvir/ritonavir. After stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory effect of nirmatrelvir/ritonavir is predicted to mostly disappear after 3 days.
Description:
Coadministration is contraindicated due to increased plasma concentrations of simvastatin; thereby, increasing the risk of myopathy including rhabdomyolysis. HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as simvastatin, are expected to have markedly increased plasma concentrations when coadministered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is contraindicated.
Paxlovid Summary of Product Characteristics, Pfizer Ltd, January 2022.

Co-administration may increase simvastatin concentrations. Co-administration contraindicated due to potential for myopathy including rhabdomyolysis. Discontinue use of simvastatin at least 12 hours prior to initiation of Paxlovid.
Paxlovid FDA Emergency Use Authorisation, Pfizer Inc, December 2021.

- https://www.med.umich.edu/asp/pdf/outpatient_guidelines/Paxlovid-DDI.pdf

Drug class	Recommendation (inhibition resolves approximately 3 days after Paxlovid is discontinued. Unless otherwise stated, **hold** means a medication should be stopped for **8 days** from the first dose of Paxlovid. **Very sensitive or narrow therapeutic index CYP3A4 drugs** may need to be restarted **10 days** after the first dose of Paxlovid)
Statins	
Atorvastatin	Hold atorvastatin
Lovastatin	Hold lovastatin
Rosuvastatin	Hold rosuvastatin
Simvastatin	Hold simvastatin

Paxlovid Drug-Drug Interactions: Liverpool (cont.)

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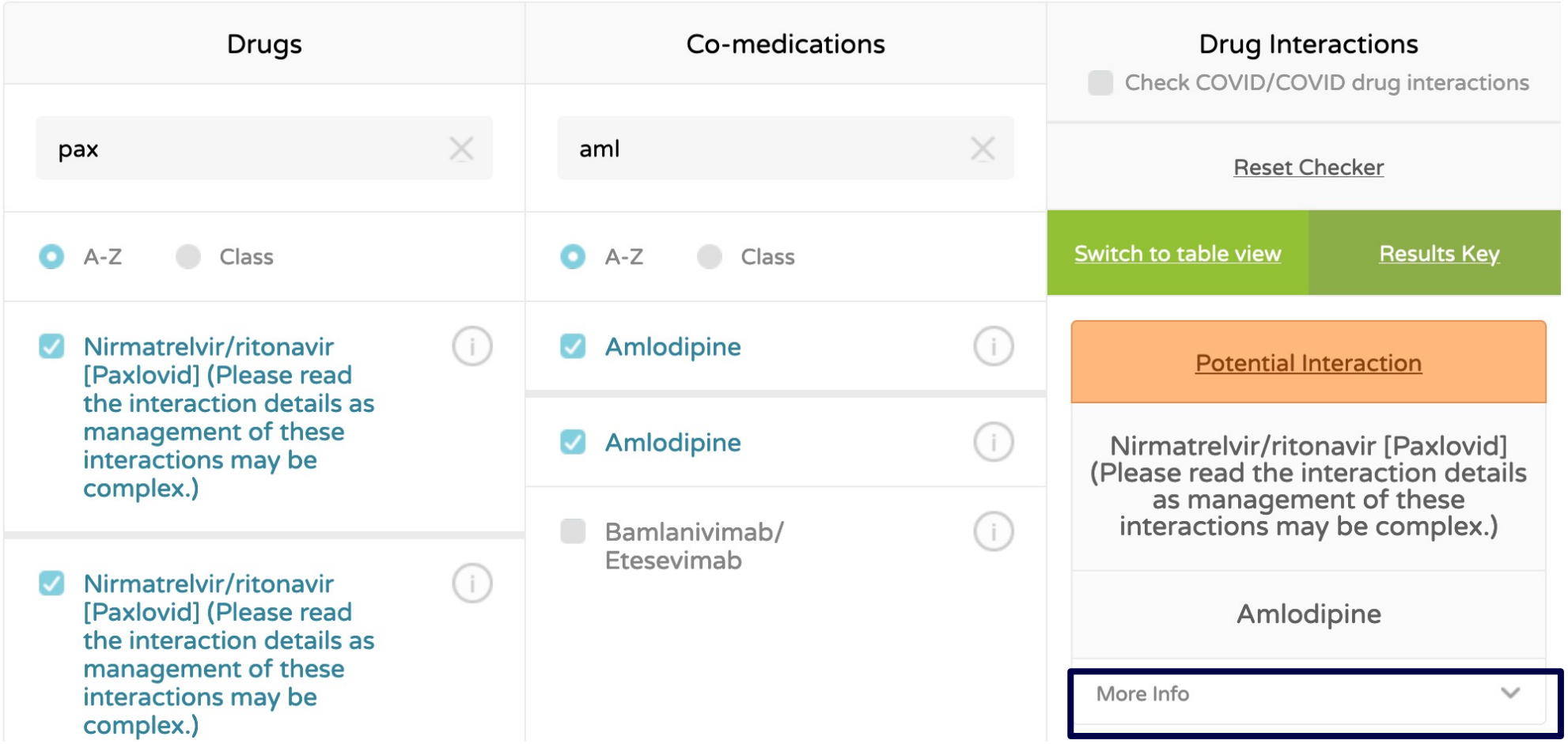
https://www.covid19-druginteractions.org/



Paxlovid Drug-Drug Interactions: Liverpool (cont.)

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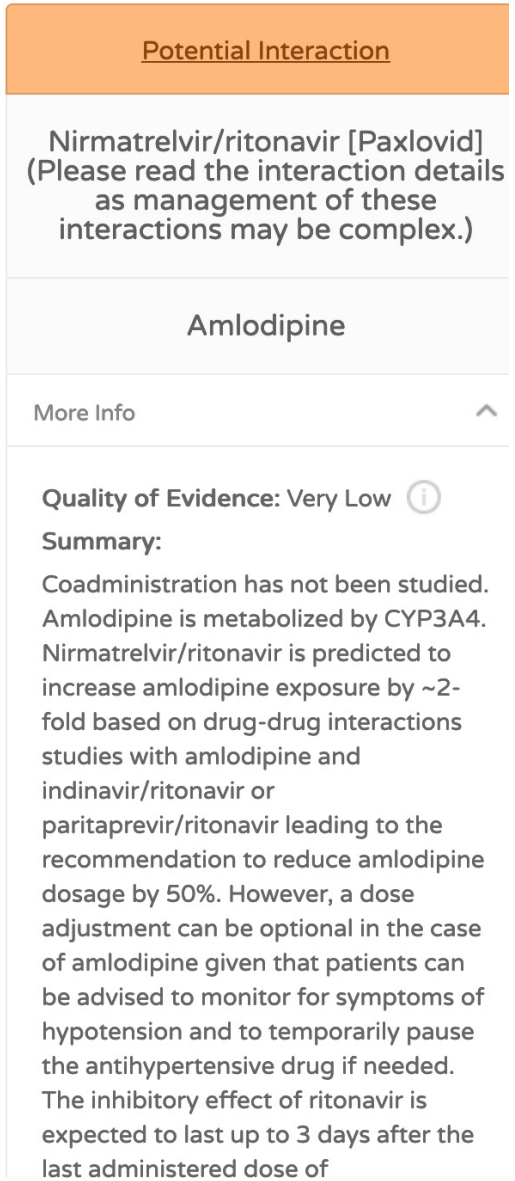
https://www.covid19-druginteractions.org/



Link to DDI Table

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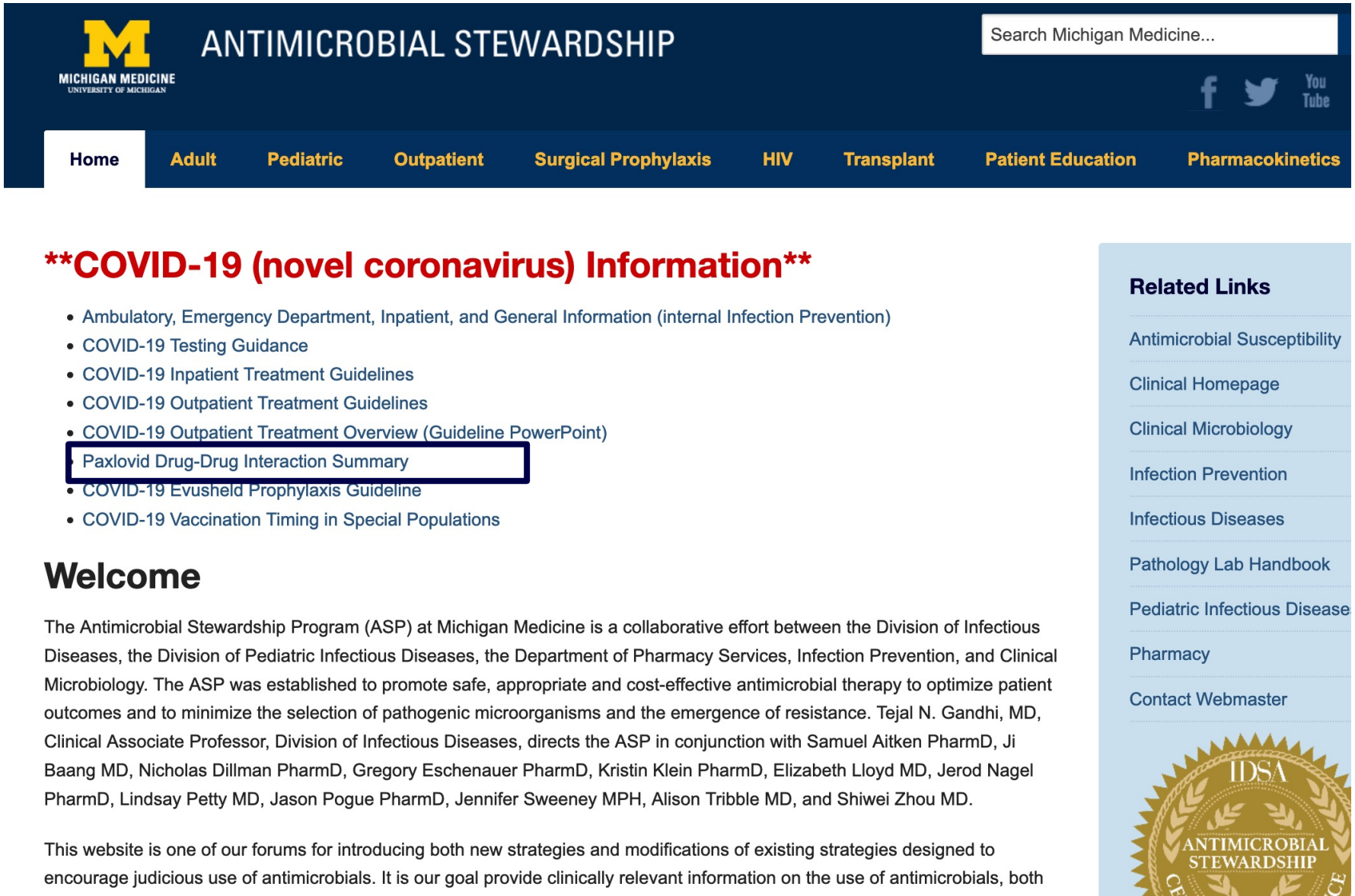
https://www.med.umich.edu/asp



Paxlovid Drug-Drug Interactions (cont.)

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- https://www.med.umich.edu/asp/pdf/outpatient_guidelines/Paxlovid-DDI.pdf

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MANAGEMENT OF PAXLOVID DRUG-DRUG-INTERACTIONS

This list is not meant to be all inclusive. Drug-drug interactions can be checked more completely at Liverpool COVID-19 Drug-Drug Interaction website. Please view **Appendix B** to identify preferred pharmacist to contact for questions.

Drug class	Recommendation (inhibition resolves approximately 3 days after Paxlovid is discontinued. Unless otherwise stated, **hold** means a medication should be stopped for **8 days** from the first dose of Paxlovid. **Very sensitive or narrow therapeutic index CYP3A4 drugs** may need to be restarted **10 days** after the first dose of Paxlovid)
Antibiotics	
Rifampin	Do not use Paxlovid
Rifapentine	Do not use Paxlovid
Alpha-1 blockers	
Alfuzosin	Hold alfuzosin
Silodosin	Hold solodosin
Tamsulosin	Hold tamsulosin
Anti-arrhythmic (other than sotalol)	
Amiodarone	Do not use Paxlovid
Disopyramide	Do not use Paxlovid
Dofetilide	Do not use Paxlovid
Dronaderone	Do not use Paxlovid
Flecainide	Do not use Paxlovid
Mexilitine	Do not use Paxlovid
Propafenone	Do not use Paxlovid
Quinidine	Do not use Paxlovid
Anti-epileptics	
Carbamazepine	Do not use Paxlovid

Paxlovid Drug-Drug Interactions (cont.)

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- For more complex DDIs or narrow therapeutic index interactions (i.e. Tacrolimus)
  - Prefer mAb if available
  - Discuss with their specialist if possible

Paxlovid Drug-Drug Interactions (cont.)

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Common Absolute Contraindications:

- St John's Wart
- Amiodorone
- Rivaroxaban
- Carbamazepine
- Clozapine

Common holding or dose adjustments needed:

- Simvastatin (hold)
- Oxycodone (reduce)
- Amlodipine (reduce)
- Sildenafil (hold if used for ED)
- Tamulosin (hold)

Molnupiravir MD Decision-Making Process

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- Less efficacious—second-line alternative agent
  - 30% risk reduction in hospitalization and death

1. Eligibility Criteria:
   - Up-to-date with vaccines:
     - Age ≥ 75
     - Age 65-64 + risk factor
   - Alternative agent if Pax or mAb not available or contraindicated:
     - Moderate to severe immunocompromise regardless of vaccine status (any age)
     - Age ≥65 and ***not*** up-to-date w/vaccines
     - Age <65 not up-to-date w/vaccines and w/one priority risk factor
2. Symptoms ≤ 5 days
3. Age ≥ 18
4. Renal Function, Liver Function: no adjustments or contraindications

Molnupiravir MD Decision-Making Process

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5. Pregnancy – contraindicated
6. DDI: None
7. Consent:
   - Review the following with the patient:
     - Potential adverse events: diarrhea, nausea, dizziness
     - Pregnancy contraindication, and EUA status with patient (details in EUA for healthcare providers)
     - Provide electronically the FDA Fact Sheet for Patients/Caregivers via email or patient portal:
     - Fact Sheet molnupiravir
8. Meijer Location for your patient

- $0 co-pay to patients

Molnupiravir MD Decision-Making Process

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- Molnupiravir 800mg (4x 200mg) po bid x 5 days
- Available at **ALL** Meijer pharmacies
- Send eRx in MiChart to Meijer pharmacies. In script, document that the patient has:
  - Positive test
  - Date of symptom onset
  - Specific reason for eligibility (i.e. immunocompromised, Lupus on cellcept and prednisone)

Summary- **When prescribing think about:**

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1. Eligibility Criteria → Comorbidities
2. Day of symptom onset = Treatment window
3. Age, weight
4. Renal Function, Liver Function
5. Pregnancy
6. DDI if Paxlovid
   - Liverpool is your friend
   - Many DDIs can be managed with adjustments
   - Important to get more patients on the most efficacious drug possible
7. Patient consent and EUA FAQ
8. Meijer Location (or available FQHC) for your patient

Practical Tips for Oral COVID-19 Therapeutic Prescribing

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